

## Amendments to the Claims:

1-20. (Canceled).

21. (Currently Amended) A method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B, and the binding specificity is ~~an change in~~ intramolecular binding affinity of the PAS domain, detected as a change in chemical shifts detected by <sup>1</sup>H/<sup>15</sup>N-HSQC NMR, wherein PAS refers to Per-ARNT-Sim, ARNT refers to acyl hydrocarbon receptor nuclear translocator, and HIF2a refers to hypoxia inducible factor 2 alpha.

22. (Currently Amended) A method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B and is present as part of HIF2a, and the binding specificity is ~~an change in~~ intermolecular binding affinity of the PAS domain detected as a change in transcription complex formation of DNA: the HIF-2a: ARNT.